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ORIGINAL ARTICLE

Seroprevalence of hepatitis virus infection in men who have sex with men aged 18–40 years in Taiwan

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Background/Purpose: Men who have sex with men (MSM) are at increased risk for hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infections than the general population. Comparisons of the seroprevalence rates of these hepatitis viruses between HIV-positive and HIV-negative MSM are rarely performed in Taiwan.

Methods: Between January 2009 and June 2010, data on the serologies for HAV, HBV, and HCV were collected from two groups of patients: HIV-negative MSM, aged 18–40 years, who sought voluntary counseling and testing (VCT) for HIV infection, and HIV-positive MSM of the same age group who sought HIV care at the National Taiwan University Hospital. Both groups of patients were also tested for syphilis.

Results: During the 18-month study period, 690 HIV-negative MSM and 438 HIV-positive MSM were enrolled and tested for anti-HAV antibody, HBV surface antigen (HBsAg), hepatitis B core antibody (anti-HBc antibody), and anti-HCV antibody. HIV-positive MSM were older than HIV-negative MSM (30.5 $\pm$ 5.4 vs. 25.8 $\pm$ 4.7 years, $p < 0.01$). For HIV-positive MSM, the mean CD4 lymphocyte count was 477.6 $\pm$ 230.0 cells/μL and 46% of them had undetectable plasma HIV RNA load ($<$ 40 copies/mL by reverse transcription-polymerase chain reaction assay). The overall seroprevalence rates of HAV, HBsAg, and HCV in HIV-positive MSM were 15.1%, 16.4%,

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and 5.5%, respectively, while in HIV-negative MSM, they were 7.4%, 6.2%, and 0.4%, respectively. In the multivariate analysis, age was significantly associated with seropositivity for HAV (OR [per one age group increase]: 1.96; 95% CI: 1.6—2.5), HBsAg (OR: 2.02; 95% CI: 1.6—2.6), anti-HBc (OR: 2.68; 95% CI: 2.3—3.2), anti-HCV (OR: 1.67; 95% CI: 1.0—2.7), and anti-HBs (OR: 1.25; 95% CI: 1.0—1.5). HIV infection was associated with seropositivity for HBsAg (OR: 1.73; 95% CI: 1.1—2.7), anti-HBc (OR: 2.44; 95% CI: 1.8—3.3), HCV (OR: 8.91; 95% CI: 2.5—31.4), and syphilis (OR: 11.21; 95% CI: 6.7—18.9).

Conclusion: HIV-positive MSM have a higher seroprevalence rate of HBV and HCV infection than HIV-negative MSM in Taiwan. Vaccination and safe-sex counseling should be provided to prevent the transmission of hepatitis viruses among MSM who may be engaged in high-risk behaviors.

Introduction

Men who have sex with men (MSM) are at increased risk for sexually transmitted diseases (STD), such as chlamydia, gonorrhea, syphilis, hepatitis A virus (HAV) infection, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and human immunodeficiency virus (HIV) infection, than the general population.[1—3] Nevertheless, the risk for hepatitis virus infections among MSM will vary with regions of different endemicities of hepatitis virus infections studied and the extent to which vaccination programs are implemented for vaccine-preventable hepatitis viruses, such as HAV and HBV.

Taiwan used to be hyperendemic for HBV infection before implementation of a nationwide HBV vaccination program since July 1984.[4] For persons born before 1984, the prevalence of chronic HBV infection was estimated 15—20% among adults, which declines significantly as well as hepatocellular carcinoma among those born after 1986 in serial surveillance studies, regardless of HIV serostatus.[5—7] In contrast to HBV, there is no nationwide HAV vaccination in Taiwan, though HAV vaccination is provided free-of-charge to aborigines[8] and is recommended to those who are at risk for infection. With improvements in sanitation in Taiwan, HAV seroprevalence has significantly declined in younger populations.[9,10] Although MSM have a higher HAV seroprevalence than heterosexuals in Western countries,[11,12] a recent study in Taiwan demonstrated that the only factor that was associated with anti-HAV seropositivity was age, and HIV serostatus was not independently associated with anti-HAV seropositivity.[9]

In Taiwan, the prevalence of HCV is estimated at 4—10% in the general population[6,13] and 30—56% in HIV-positive patients in studies that included different proportions of injecting drug users (IDUs).[14—16] After an outbreak of HIV infection occurred among IDUs in Taiwan between 2003 and 2007, HCV seropositivity was 95—97% among HIV-positive IDUs.[9,14,17,18] While HCV transmission is significantly more efficient among IDUs than among MSM, an increasing number of reports have indicated that HCV infections are presenting among MSM who may be engaged in risky sexual contact.[19—27]

In this study, we aim to compare the seroprevalence rates of HAV, HBV, and HCV between HIV-positive MSM and HIV-negative MSM aged between 18—40 years.

Patients and methods

Setting and study population

This seroprevalence study was conducted at the National Taiwan University Hospital, the major referral hospital for inpatient and outpatient HIV care, which serves as the largest site for the provision of voluntary counseling and testing (VCT) for HIV in Taiwan. As a response to the HIV epidemic in Taiwan, the VCT program was implemented in 1990. In addition to HIV, serologic tests for *Treponema pallidum*, HAV (anti-HAV IgG antibody), HBV (hepatitis B surface antigen [HBsAg], anti-HBs antibody, and hepatitis B core antibody [IgG anti-HBc antibody]), HCV (anti-HCV antibody), and *Entamoeba histolytica* (indirect hemagglutination antibody [IHA]) have also been provided as VCT services at this hospital since 2006.[28] In this study, MSM aged between 18 and 40 years were enrolled when they sought VCT for HIV infection between January 2009 and June 2010. Because few MSM who were also IDUs were identified, they were excluded from this study. VCT clients were given a unique code as an identifier that consisted of his birth year and the initial letter and last four digits of his identification (ID) card number. The initial letter of the ID number indicated the birth place of the subjects.

For HIV-positive MSM, serology for the hepatitis viruses, syphilis, CD4 lymphocyte count, and plasma HIV RNA load were performed as routine assessments among HIV-infected MSM when they sought HIV care, and the data was recorded using a standardized case collection form. A titer of rapid plasma reagin (RPR) $\geqq$ 4 in this study would be recorded as syphilis if *T pallidum* hemagglutination (TPHA) was tested positive. The study was approved by the research ethics committee of the hospital and was waived for informed consent.

Laboratory investigations

Determination of anti-HAV antibody status in the serum samples obtained from HIV-negative MSM were performed at the VCT site using Hepavase A96 TMB, by following the instructions of the manufacturer (General Biologicals Corp., Hsin-Chu, Taiwan), which reported sensitivity of 99.8% and specificity of 99.5%. For HIV-positive MSM, anti-

HAV antibody was determined at the central laboratory of the hospital with the use of chemiluminescent microparticle immunoassay (CMIA) (Architect® HAVAb-IgG, Abbott Diagnostic Division, Germany). Consistency between the two test kits for detection of the anti-HAV antibody was assessed using the first 217 blood samples from HIV-negative and HIV-positive patients, and only two revealed discordant results, indicating the consistency is higher than 99%.

HBsAg, anti-HBs antibody, and IgG anti-HBc antibody were determined with the use of enzyme immunoassays (Abbott Laboratories). Antibodies to HCV were determined with the use of a third-generation enzyme immunoassay (Ax SYM HCV III, Abbott Laboratories). Anti-HIV antibodies were determined using particle agglutination (SFD HIV 1/2 PA; Bio-Rad FUJIREBIO, Japan) and confirmed using Western blot (MP Diagnostics HIV BLOT 2.2.; MP Biomedicals Asia Pacific Pte Ltd, Singapore). Syphilis serology was tested using RPR card antigen suspension (Macro-Vue RPR Card Tests; BD, NJ, USA).

Plasma HIV RNA loads were quantified using reverse transcription-polymerase chain reaction (RT-PCR) assay (Roche Amplicor, version 1,5; Roche Diagnostics, Branchburg, NJ, USA) with a lower detection limit of 40 (1.6 $\log_{10}$) copies/mL. CD4 counts were determined using FACFlow (BD FACS Calibur; Becton Dickinson, San Jose, CA, USA).

Table 1 Demographics and seroprevalence of hepatitis viruses in HIV-positive and -negative MSM aged 18—40 years.

	HIV-positive	HIV-negative
No. of subjects	438	690
Mean ± SD, y	30.5 ± 5.4	25.8 ± 4.7
Age, y		
18—22, *n* (%)	33 (7.5)	198 (28.7)
23—27	101 (23.1)	262 (38.0)
28—33	163 (37.2)	183 (26.5)
34—40	141 (32.2)	47 (6.8)
Positive anti-HAV antibody, *n*/*N* (%)	66/438 (15.1)	51/690 (7.4)
Positive HBsAg, *n*/*N* (%)	70/428 (16.4)	43/690 (6.2)
Positive anti-HBc, *n*/*N* (%)	221/418 (52.9)	140/690 (20.3)
Positive anti-HCV antibody, *n*/*N* (%)	24/434 (5.5)	3/689 (0.4)
RPR	115/429 (26.8)	32/690 (4.6)

Note: *n*/*N* = number of patients with positive test result/number of patients with test results.
Abbreviations: HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; RPR, rapid plasma reagin; SD, standard deviation.

Statistical analysis

All statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL, USA). Categorical variables were compared using Fisher's exact test or the Chi-square test. Noncategorical variables were compared using the Mann-Whitney U test. Factors with p value <0.2 were included for multivariate analysis. Multiple logistic regression analyses were separately used to determine the factors associated with seropositivity for HAV, HBV, and HCV. All comparisons were two-tailed and a p value <0.05 was considered significant.

Results

During the 18-month study period, 438 HIV-positive MSM and 690 HIV-negative MSM, who were between 18—40 years of age, were enrolled. Their characteristics are shown in Table 1. The mean age of HIV-positive MSM and HIV-negative MSM were 30.5 ± 5.4 and 25.8 ± 4.7 years, respectively ($p < 0.001$); 69.4% of HIV-positive MSM were >27 years, while only 33.3% of HIV-negative MSM were >27 years ($p < 0.001$). For HIV-positive MSM, the mean CD4 lymphocyte count was 477.6 ± 230.0 cells/μL, with 88.6% having a CD4 count >200 cells/μL and 46% an undetectable plasma HIV RNA load (< 40 copies/mL by RT-PCR) when this study was conducted (Table 1).

HIV-positive MSM had a significantly higher overall prevalence of positive anti-HAV antibody (15.1% vs. 7.4%, $p < 0.001$), HBsAg (16.4% vs. 6.2%, $p < 0.001$), anti-HBc (52.9% vs. 20.3%, $p < 0.001$), and anti-HCV (5.5% vs. 0.4%, $p < 0.001$) than HIV-negative MSM (Table 1). In the subgroup analysis of persons born after 1986 (age: 18—22 years), we found that positive anti-HBc antibody was not statistically significantly associated with HIV infection (6.5% vs. 7.1%, $p = 0.99$), while among persons born before 1986, positive anti-HBc antibody was statistically significantly associated with HIV infection (56.3% vs. 29.4%, $p < 0.001$). In the multivariate analysis, we found that, compared with HIV-negative MSM, HIV-positive MSM were associated with a higher risk for seropositivity for HBsAg (odds ratio [OR]: 1.73; 95% CI: 1.1—2.7), anti-HBc (OR: 2.44; 95% CI: 1.8—3.3), HCV (OR: 8.91; 95% CI: 2.5—31.4), and syphilis (OR: 11.21; 95% CI: 6.7—18.9).

Compared with HIV-positive MSM born before 1986, HIV-positive MSM born after 1986 had a significantly lower prevalence of HBsAg (3% vs. 17.5%, $p = 0.03$) and anti-HBc (6.5% vs. 56.3%, $p < 0.001$). HIV-negative MSM born after 1986 also had a significantly lower prevalence of HBsAg (1.5% vs. 8.1%, $p = 0.001$) and anti-HBc (7.1% vs. 25.61%, $p < 0.001$) than HIV-negative MSM born before 1986. Positive anti-HBs status alone, with negative HBsAg and negative anti-HBc, among HIV-negative and HIV-positive MSM was 67.1% (369/550) and 68.6% (131/191), respectively ($p = 0.7$). Positive anti-HBs status alone among HIV-negative and HIV-positive MSM born after 1986 were 52.3% (103/197) and 55.2% (16/29), respectively ($p = 0.77$).

The seroprevalence of each hepatitis virus was associated with age. The relationship between age and seropositivity for hepatitis virus infections are shown in Fig. 1. The seropositivity for HAV was increased significantly in patients >30 years. In the multivariate analysis, we found that, after adjusted with HIV infection, age was significantly associated with seropositivity for anti-HAV (OR (per each age group increment): 1.96; 95% CI: 1.6—2.5), HBsAg (OR: 2.02; 95% CI: 1.6—2.6), anti-HBc (OR: 2.68; 95% CI: 2.3—3.2), anti-HCV (OR, 1.67; 95% CI: 1.0—2.7), and anti-HBs alone (OR: 1.25; 95% CI: 1.0—1.5) (all $p < 0.05$).

We also analyzed the distribution of birth places, and these results are shown in Fig. 2 and Table 2. While we did not record their past or current residencies after birth,

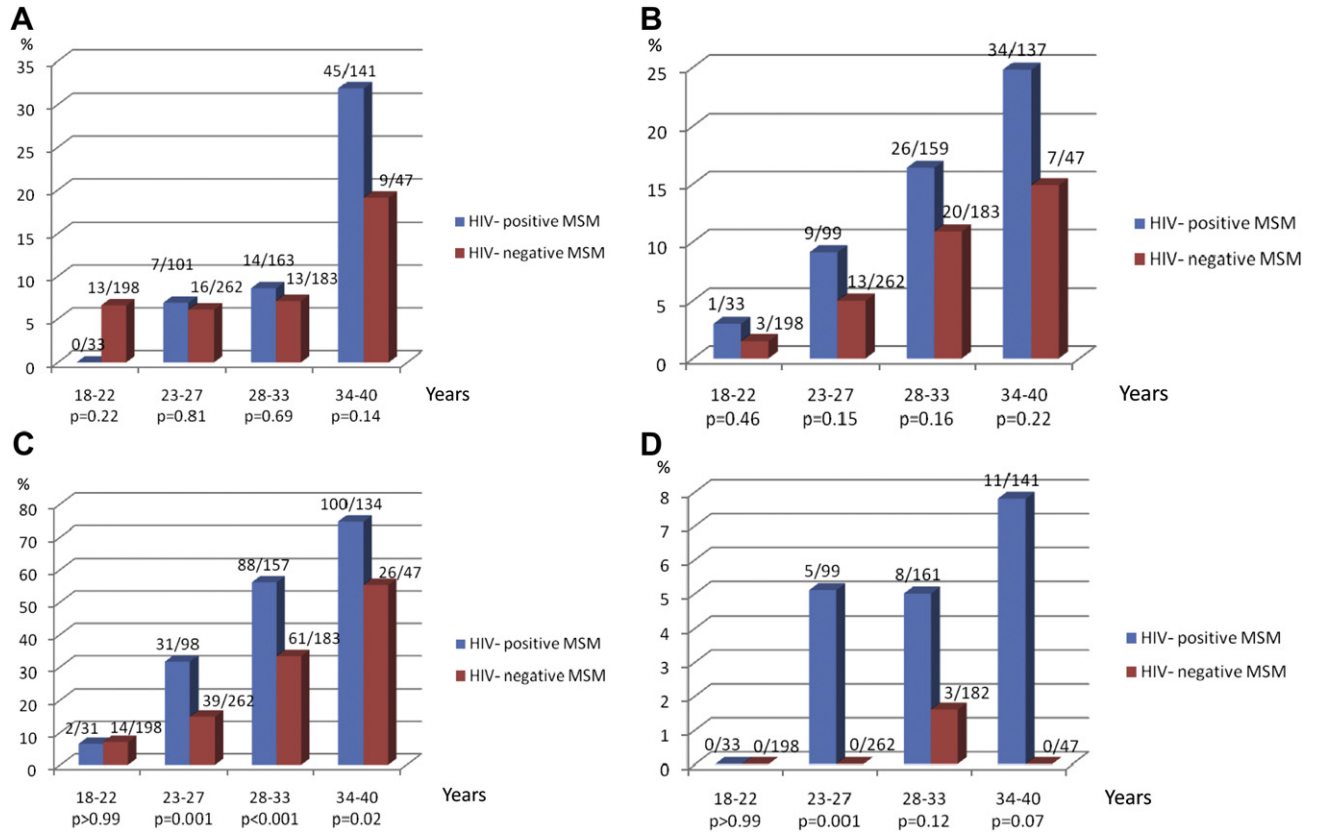

Figure 1 A. Relationship between age and hepatitis A virus seropositivity. The *p* values indicate comparisons between HIV-positive and -negative MSM in the same age group. B. Relationship between age and HBsAg seropositivity. C. Relationship between age and anti-HBc seropositivity. D. Relationship between age and HCV seropositivity.

51.7% (583/1128) were born in Taipei (Taipei City and New Taipei City) (Table 2). There were no statistically significant differences in terms of HAV seroprevalence between patients who were born in Taipei and those who were not born in Taipei (45/503 vs. 72/625, $p = 0.16$) or between the patients born in northern Taiwan and those born in other parts of Taiwan (67/701 vs. 50/427, $p = 0.25$) (Fig. 2B).

Discussion

In this survey conducted among MSM who were aged <40 years in metropolitan Taipei city, we found that HIV-positive MSM had a higher seroprevalence of HAV, HBV, and HCV infection than HIV-negative MSM. After adjustment for HIV serostatus, we found that age was associated with seropositivity for HBV and HCV infections.

In the published studies conducted in developed countries,[9,12,14,29,30] the seroprevalence of HAV infection is higher among HIV-positive persons than HIV-negative persons, and IDUs have the highest seroprevalence rate for HAV infection. The differences in HAV seroprevalence between different studies from developed countries may be related to the age and risk group for HIV transmission of the study populations and endemicity of HAV infection at the study sites because IDU and older age are associated with a significantly higher HAV seroprevalence.[9] In this study, the HAV seroprevalence among MSM aged < 40 years is 10.4%, which is similar to a survey among military recruits with similar gender and age groups in the United states in 2007,[31] but is higher than that among the general population in Finland[32] and lower than other Asian countries, such as Korea, where similar trends of HAV seroprevalence are also noted.[33] Compared with the HAV seroprevalence rates in different age groups of MSM reported in our previous study,[9] we found that HAV seroprevalence decreased further in this study. We also found that HIV-positive MSM have a higher HAV seroprevalence than HIV-negative MSM (15.1% vs. 7.4%, $p < 0.01$); however, we were not able to find a statistically significant association between HAV and HIV infection in the multivariate analysis. Consistent with the findings of our previous study,[9] which demonstrated that HAV seroprevalence increased with age, this study shows a rapid increase of HAV seropositivity between 28—33 years and 34—40 years (Fig. 1A).

Confounding factors of HAV seropositivity may include birth place and places of early residency. According to one recently published study by Su et al, the birth period and childhood residence areas were significantly associated with HAV seropositivity in Taiwan.[34] In this study, more than 50% of the subjects were born in Taipei (Taipei City and New Taipei City) (Table 2 and Fig. 2). While information on the early and current residencies of the subjects was not collected, there were no statistically significant differences in terms of HAV seropositivity between subjects who were born in Taipei and those who were born in other places; or

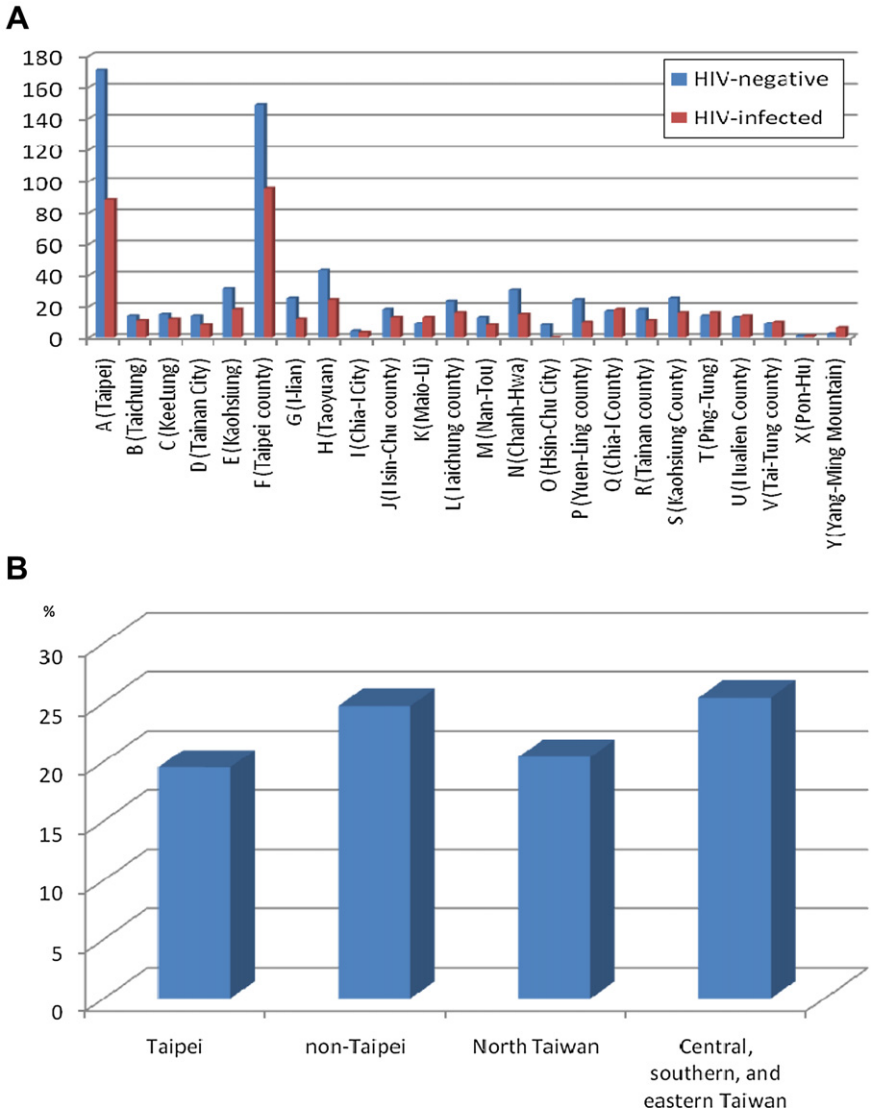

Figure 2 A. Distribution of birth places among HIV-positive and -negative subjects. B. HAV seroprevalence among HIV-positive and -negative subjects with different places of birth. No statistically significant differences were observed between patients born in Taipei ($p = 0.16$), non-Taipei regions, those born in northern Taiwan, and those born in other parts of Taiwan ($p = 0.25$).

between subjects who were born in northern Taiwan and those who were born in other parts of Taiwan (Fig. 2B). These findings should be informative for public health experts to make recommendations for the appropriate timing of HAV vaccinations in this high-risk population.

In Western countries, HBV transmission mainly occurs when persons are engaged in risky behaviors for HIV and HBV transmissions and, therefore, HIV-positive persons have a higher prevalence of HBV infection than the general population.[35] In Taiwan, where chronic HBV infection used to be hyperendemic before the implementation of a nationwide HBV vaccination program in 1984, the seroprevalence of HBsAg in HIV-positive persons (20.3%) is similar to that of the general population of the same age group[17] because most HBV infections are contracted in the perinatal period and childhood.[36,37] However, the findings of significantly higher seroprevalence rates of anti-HBc in HIV-positive MSM than HIV-negative MSM in this study, and in IDUs than in other risk groups of the same age groups by Sun et al, suggest that subsequent risky behaviors of HIV transmission still increase the risk of HBV transmission among persons who did not receive HBV vaccination or who did not have sufficient protective antibodies for HBV despite vaccination.[15] In the study by Sheng et al,[38] the incidence of HBV infection among HIV-infected persons who were seronegative to all HBV markers was estimated at 9.69 per 100 person-years of follow-up, which argues strongly for HBV vaccination in MSM who are nonimmune to HBV infection.

This study demonstrates the effectiveness of HBV vaccination in both HIV-positive and -negative MSM. Compared with HIV-positive MSM born before 1986, HIV-positive MSM born after 1986 have a significantly lower prevalence of HBsAg (3% vs. 17.5%) and anti-HBc (6.5% vs. 56.3%). Likewise, HIV-negative MSM born after 1986 have a significantly lower prevalence of HBsAg (1.5% vs. 8.1%) and anti-HBc (7.1% vs. 25.6%) than HIV-negative MSM born before 1986. The HBV seroprevalence in MSM of the youngest age group is similar to that reported by Lu et al in persons of high-school

Table 2 Distribution of birth place and seroprevalence of HAV among HIV-positive and -negative MSM.

		Anti-HAV-positive	Anti-HAV-negative	*P*
Taipei[a]	HIV-positive	23	160	
	HIV-negative	22	298	
	Total	45	458	
Non-Taipei	HIV-positive	43	212	
	HIV-negative	29	341	
	Total	72	553	0.16
Northern Taiwan[b]	HIV-positive	34	229	
	HIV-negative	33	405	
	Total	67	634	
Central, southern, and eastern Taiwan[c]	HIV-positive	32	143	
	HIV-negative	18	234	
	Total	50	377	0.25

[a] Taipei City and New Taipei City.
[b] North Taiwan: Taipei City, New Taipei City, Keelung, I-Lan, Taoyuan, Miao-Li, Hsin-Chu City and County, Yang-Ming Mountain.
[c] Taichung City, Tainan City, Kaohsiung City, Nan-Tou, Chang-Hwa, Yun-Lin County, Ping-Tung, Hualien, Tai-Tung, and Off-Shore islands.

or college age who had received HBV vaccination at birth.[39] Besides, according to the report by Ni et al, the seroprevalence rate of HBsAg among persons aged 15–20 years was 7% in 1999, and anti-HBc, which represents HBV infection, was 20.6% of persons aged 15–20 years in 1999.[40]

In this study, we did not obtain data on the seroprevalence of hepatitis viruses in the general population for comparison purposes. In our previous study, the seroprevalence of HBsAg and anti-HBc was compared between HIV-positive and HIV-negative persons born before 1984.[17] Compared with HIV-negative persons born before July 1984, HIV-positive persons born before July 1984 had a significantly higher seroprevalence of HBsAg (20.3% vs. 15.5%, $p < 0.001$) and anti-HBc (78.9% vs. 72.1%, $p < 0.001$).[17] In addition, a significant decline in HBV seroprevalence among both HIV-negative and -positive persons born in the era of the nationwide HBV vaccination in Taiwan has also been shown.[17] In this study, positive anti-HBs status alone, which indicates the prevalence of HBV vaccination-related protection, among HIV-negative and -positive MSM were 67.1% and 68.6%, respectively. Both rates are higher than that reported by Lu et al for persons of high-school or college age born after 1986 and received HBV vaccination at birth.[39] In HIV-positive patients, the anti-HBs antibody titer may decline with age and immunodeficiency.[41] The higher prevalence of anti-HBs positivity among MSM may be related to natural boosters acquired through high-risk sexual contact, although more behavioral studies are needed to confirm this hypothesis.

Sharing contaminated needles and solvent is an efficient route for HCV transmission, which lends explanations to the extremely high HCV seroprevalence among IDUs who acquired HIV infection in Taiwan between 2003–2007.[18,42] With the implementation of a harm-reduction program by providing clean needles and methadone to IDUs, HIV infections among IDUs significantly declined. In recent years, outbreaks of sexually transmitted, acute, or recent HCV infections have raised concern in several European countries.[19–24,43] In the Netherlands, where the prevalence of HCV in HIV-infected MSM has been on the rise since the mid-1990s,[25] sexual practices that lead to rectal bleeding and the use of snorting drugs were identified as risk factors for acute HCV infection.[26] In this study, we found that HCV seroprevalence was significantly higher in HIV-positive MSM than HIV-negative MSM (5.5% vs. 0.4%) (Fig. 1D) and HIV infection and age were statistically significantly associated with HCV seropositivity. In a recent investigation, we also found an increased incidence of recent HCV infections among non-IDU, HIV-infected patients between 1994–2010, and recently syphilis was identified as an independent risk factor for HCV infection.[27] These findings should alert healthcare providers to the continued risk of the transmission of HCV among MSM, and safe-sex counseling should be consistently provided.

There are several limitations to this study. First, the persons who seek VCT services at our hospital and HIV-infected persons seeking HIV care at our outpatient clinics may not be representative of the whole MSM population in Taiwan, although the annual number of VCT provided by this hospital accounts for one-fourth of the total number of VCT provided at the designated hospitals for HIV care around Taiwan. Second, the cross-sectional study design precludes us from estimating the incidences of HAV, HBV, and HCV infection among MSM. Third, we did not collect data on socioeconomic status or history of HAV and HBV vaccinations, although offering HAV vaccination was not a common practice in Taiwan and the HBV vaccine coverage rate is higher than 98% among persons < 22 years.[39,40] Fourth, although we found that age was an independent risk factor of seropositivity for anti-HAV, HBsAg, anti-HCV, and amount of risky exposure may limit interpretation of our findings. Fifth, we did not further examine the seroprevalence of hepatitis D virus (HDV) among HBsAg-positive MSM in this age range, although our recent study revealed that HDV seroprevalence among HIV-infected non-IDUs and HIV-uninfected non-IDUs who were also HBsAg-positive was 9.3% and 2.3%, respectively.[44]

We conclude that HIV-positive MSM have a higher seroprevalence of HBV and HCV infection than HIV-negative MSM in Taiwan. Vaccination and safe-sex counseling should be provided to prevent the transmission of hepatitis viruses among MSM who may be engaged in high-risk behaviors.

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